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REVIEW

GnRHa trigger for final oocyte maturation: is HCG trigger history?

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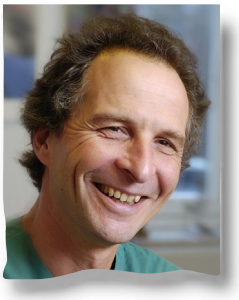

Peter Humaidan is a Professor at The Fertility Clinic at Skive Regional Hospital and Faculty of Health Aarhus University, Denmark. His scientific work has focused on developing individualized treatment protocols for the infertile patient, specifically exploring the role of LH during the follicular and luteal phases of the stimulated cycle. His main fields of interest are triggering of ovulation with GnRH agonist, use of GnRH antagonists, and ovarian hyperstimulation syndrome prevention. He is the founder of the international society 'The Copenhagen GnRHa Triggering Workshop Group'. He has a wide international scientific network and lectures frequently at international conferences.

Abstract Since the introduction of the gonadotrophin-releasing hormone analogues (GnRHa) protocol, it has become possible to trigger final oocyte maturation with a bolus of GnRHa. This leads to a significant reduction or complete elimination of ovarian hyperstimulation syndrome compared with human chorionic gonadotrophin (HCG) trigger. Early trials showed a severe luteal phase insufficiency after GnRHa trigger despite the application of standard luteal phase support protocols. Subsequent research has led to modifications of the luteal phase support, resulting in reproductive outcome comparable to that seen after HCG trigger in normal- and high-responders. GnRHa trigger facilitates a tailored approach to subsequent luteal phase support, taking into account the ovarian response to stimulation. In the future, GnRHa is likely to be used for trigger in all women co-treated with GnRH antagonists.

KEYWORDS: GnRHa, HCG, IVF, luteal phase support, OHSS, ovulation trigger

Introduction

For decades, a bolus of 5000–10,000 IU human chorionic gonadotrophin (HCG) has successfully been used to trigger final oocyte maturation and ovulation as a surrogate for the endogenous mid-cycle surge of LH because its actions are similar to those of endogenous LH. The extended half-life of HCG (Weissman et al., 1996), however, leads to a prolonged luteotrophic effect, which increases the risk of developing ovarian hyperstimulation syndrome (OHSS) (Delvigne and Rozenberg, 2002). Moreover, the supra-physiological luteal phase steroid levels (oestradiol and progesterone) induced by the prolonged LH-like actions of HCG, have been negatively associated with oocyte quality and endometrial receptivity (Evans and Salamonsen, 2013; Forman et al., 1988; Valbuena et al., 2001).

Early studies investigated the use of a bolus of GnRHA to find a more physiological trigger, and to reduce the incidence of OHSS (Gonen et al., 1990; Itskovitz-Eldor et al., 1998). The long GnRHa pituitary down-regulation protocol was later introduced before IVF/ICSI treatment (Porter et al., 1984); however, the GnRHa trigger could not be used in women

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down-regulated with GnRHa, and was more or less forgotten. With the introduction of the GnRH antagonist protocol, the GnRHa trigger again became feasible, and new and larger trials explored this concept. From those early trials, it became evident that, although retrieval of mature oocytes led to the development of embryos with normal implantation potentials, a severe luteal phase insufficiency resulted in unacceptably high early pregnancy losses and low ongoing pregnancy rates (Griesinger et al., 2007; Humaidan et al., 2005; Kolibianakis et al., 2005). Importantly, the luteal phase insufficiency was not overcome by use of a standard luteal phase support.

Luteal phase problems have prompted suggestions of freezing all embryos after GnRHa trigger, followed by frozen–thawed embryo transfer (segmentation) in subsequent, preferably natural cycles (Devroey et al., 2011). Others have focused on 'rescuing' the luteal phase insufficiency so that a fresh transfer can be carried out. Over the years, two different luteal rescue concepts have emerged: HCG rescue and intensive luteal steroid rescue (oestradiol and progesterone). The former introduces a small bolus of HCG either on the day of oocyte retrieval (Humaidan, 2009; Humaidan et al., 2006a, 2010, 2013a; Iliodromiti et al., 2013a) or on the day of GnRHa trigger – so called 'dual trigger' (Griffin et al., 2012a; Shapiro et al., 2008, 2011a). The HCG rescue strategy has been shown to be effective in producing pregnancy rates comparable to those of HCG trigger. Clinical outcomes after intensive luteal steroid support is still controversial, with some investigators reporting good results (Engmann et al., 2008; Griffin et al., 2012a; Iliodromiti et al., 2013b; Imbar et al., 2012). Others, however, have not been able to reproduce the abovementioned results (Babayof et al., 2006; Orvieto, 2012; Orvieto et al., 2006).

As GnRHa trigger significantly reduces and, in most cases, virtually eliminates the risk of OHSS, the concept has gradually found its way into daily clinical practice (De Ziegler and Shoham, 2013). Until now, GnRHa trigger has primarily been used for women at risk of developing OHSS, In many cases, it is followed by a 'freeze all' policy. The current handling of the luteal phase after GnRHa trigger, however, still allows fresh transfer in some women at high risk of OHSS, with excellent reproductive outcomes (Humaidan et al., 2010, 2013a). Moreover, apart from the decrease in, or practical elimination of OHSS, some studies have reported retrieval of more metaphase II oocytes after GnRHa trigger compared with HCG trigger (Humaidan et al., 2005; Imoedemhe et al., 1991; Oktay et al., 2010). Higher patient convenience has also been reported during the luteal phase, with less distension and abdominal soreness (Cerrillo et al., 2009; Hernandez et al., 2009). In addition to the LH surge, the endogenous release of an FSH surge, as seen in GnRHa trigger, might reduce the incidence of immature oocyte syndrome for a sub-group of women, although it is different from the natural mid-cycle surge of gonadotrophins (Griffin et al., 2012a). Finally, GnRHa trigger facilitates dissociation between the ovulation trigger and the luteal phase support, allowing for individualization of the luteal phase support with either HCG, LH, oestradiol and progesterone, or a combination of the above (Castillo et al., 2010; Engmann et al., 2006; Humaidan et al., 2010, 2013a; Papanikolaou et al., 2011).

Increasing evidence supports the use of GnRHa trigger for all women undergoing IVF co-treated with a GnRH antagonist, and the time has come to challenge the gold standard HCG trigger. Women suitable for GnRHa trigger are reviewed below.

GnRHa trigger in low-risk women with ovarian hyperstimulation syndrome

Fresh transfer and luteal phase rescue with LH activity (HCG or recombinant LH)

In the largest randomized-controlled trial (RCT) to date, 266 women undergoing IVF/ICSI considered at low risk of developing OHSS (≤14 follicles ≥11 mm) on the day of trigger were randomized to either trigger with one bolus of 0.5 mgg GnRHa (buserelin) or 5.000 IU HCG (Humaidan et al., 2013a). At the time of randomization, women in the GnRHa group ($n = 125$) had developed a mean of 8.1 follicles compared with 7.7 follicles in the HCG group ($n = 141$). In the GnRHa group, the trigger was followed by two boluses of 1.500 IU HCG (i.e. one bolus of 1.500 IU HCG on the day of oocyte retrieval, and an additional bolus of 1.500 IU HCG after another 5 days). Moreover, both groups received standard luteal phase support consisting of oral oestradiol and vaginal progesterone. A non-significant difference in ongoing pregnancy rates, however, was observed for the first time between the GnRHa and HCG trigger groups in favour of GnRHa trigger (30% compared with 26% for GnRHa and HCG trigger, respectively). Two women in the GnRHa trigger group developed late-onset moderate OHSS. This justifies further exploration of the minimal amount of HCG necessary to secure the reproductive outcome without increasing the OHSS rate in women at low risk of OHSS (Humaidan et al., 2013a).

Kol et al. (2011) similarly explored GnRHa trigger in women at low risk of OHSS in a proof-of-concept study. Fifteen women undergoing IVF, who previously failed to conceive in at least one previous IVF attempt and who developed 12 follicles or fewer, were triggered with a bolus of GnRHa (triptorelin 0.2 mg), resulting in the retrieval of a mean of 6.7 oocytes. The luteal phase was supported with a total of two boluses of 1.500 IU HCG, one on the day of oocyte retrieval and an additional bolus on the day of oocyte retrieval and four days later. Importantly, no additional luteal phase support was given. A high ongoing clinical pregnancy rate of 47% (7/15) and no OHSS were reported. This was the first study to explore an HCG-based, complete exogenous progesterone-free luteal support after GnRHa trigger.

To further explore the HCG-based exogenous progesterone-free luteal phase, a pilot RCT in 90 normoresponder women undergoing IVF was recently conducted in our unit. Women were randomized to trigger with either GnRHa or HCG. Only women in the GnRHa trigger group received a daily small bolus of recombinant HCG (125 IU) subcutaneously to support the luteal phase until the day of the pregnancy test 14 days later. The HCG trigger group received standard luteal support during the same period. The ongoing pregnancy rate was 42% in the GnRHa group and 39% in the HCG trigger group (Humaidan et al., unpublished data). Results, therefore, look promising for this protocol, although larger studies are needed to explore the optimal daily dose of recombinant HCG to be used during the luteal phase.